Genome-wide analysis reveals TET- and TDG-dependent 5-methylcytosine oxidation dynamics.

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Public Summary:
TET dioxygenases successively oxidize 5-methylcytosine (5mC) in mammalian genomes to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC). 5fC/5caC can be excised and repaired to regenerate unmodified cytosines by thymine-DNA glycosylase (TDG) and base excision repair (BER) pathway, but it is unclear to what extent and at which part of the genome this active demethylation process takes place. Here, we have generated genome-wide distribution maps of 5hmC/5fC/5caC using modification-specific antibodies in wild-type and Tdg-deficient mouse embryonic stem cells (ESCs). In wild-type mouse ESCs, 5fC/5caC accumulates to detectable levels at major satellite repeats but not at nonrepetitive loci. In contrast, Tdg depletion in mouse ESCs causes marked accumulation of 5fC and 5caC at a large number of proximal and distal gene regulatory elements. Thus, these results reveal the genome-wide view of iterative 5mC oxidation dynamics and indicate that TET/TDG-dependent active DNA demethylation process occurs extensively in the mammalian genome.

Scientific Abstract:
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